



Genetics Home Reference

Your Guide to Understanding Genetic Conditions

Handbook

Help Me Understand Genetics

Mutations and Health

Reprinted from Genetics Home Reference (<http://ghr.nlm.nih.gov/>)

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Chapter 2

Mutations and Health

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What is a gene mutation and how do mutations occur?

A gene mutation is a permanent change in the DNA sequence that makes up a gene. Mutations range in size from a single DNA building block (DNA base) to a large segment of a chromosome.

Gene mutations occur in two ways: they can be inherited from a parent or acquired during a person's lifetime. Mutations that are passed from parent to child are called hereditary mutations or germline mutations (because they are present in the egg and sperm cells, which are also called germ cells). This type of mutation is present throughout a person's life in virtually every cell in the body.

Mutations that occur only in an egg or sperm cell, or those that occur just after fertilization, are called new (de novo) mutations. De novo mutations may explain genetic disorders in which an affected child has a mutation in every cell, but has no family history of the disorder.

Acquired (or somatic) mutations occur in the DNA of individual cells at some time during a person's life. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if a mistake is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed on to the next generation.

Mutations may also occur in a single cell within an early embryo. As all the cells divide during growth and development, the individual will have some cells with the mutation and some cells without the genetic change. This situation is called mosaicism.

Some genetic changes are very rare; others are common in the population. Genetic changes that occur in more than 1 percent of the population are called polymorphisms. They are common enough to be considered a normal variation in the DNA. Polymorphisms are responsible for many of the normal differences between people such as eye color, hair color, and blood type. Although many polymorphisms have no negative effects on a person's health, some of these variations may influence the risk of developing certain disorders.

For more information about mutations:

The National Cancer Institute offers a discussion of hereditary mutations (<http://www.cancer.gov/cancertopics/understandingcancer/genetesting/Slide12>) and information about acquired mutations (<http://www.cancer.gov/cancertopics/understandingcancer/genetesting/Slide13>).

The Wellcome Trust offers a brief overview of mutations and polymorphisms (http://genome.wellcome.ac.uk/doc_WTD020780.html).

The Centre for Genetics Education provides a fact sheet discussing changes to the genetic code (<http://www.genetics.com.au/factsheet/02.htm>).

For additional information about gene mutations, refer to the following resources from the University of Utah Genetic Science Learning Center:

- What is a Mutation? (<http://gslc.genetics.utah.edu/units/disorders/mutations/>)
- How do Mutations Occur? (<http://gslc.genetics.utah.edu/units/disorders/sloozeworm/>)

How can gene mutations affect health and development?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. Sometimes, gene mutations prevent one or more of these proteins from working properly. By changing a gene's instructions for making a protein, a mutation can cause the protein to malfunction or to be missing entirely. When a mutation alters a protein that plays a critical role in the body, it can disrupt normal development or cause a medical condition. A condition caused by mutations in one or more genes is called a genetic disorder.

In some cases, gene mutations are so severe that they prevent an embryo from surviving until birth. These changes occur in genes that are essential for development, and often disrupt the development of an embryo in its earliest stages. Because these mutations have very serious effects, they are incompatible with life.

It is important to note that genes themselves do not cause disease—genetic disorders are caused by mutations that make a gene function improperly. For example, when people say that someone has “the cystic fibrosis gene,” they are usually referring to a mutated version of the CFTR gene, which causes the disease. All people, including those without cystic fibrosis, have a version of the CFTR gene.

For more information about mutations and genetic disorders:

The National Cancer Institute provides additional information about how gene mutations can trigger disease:

- Gene Mutations and Disease (<http://www.cancer.gov/cancertopics/understandingcancer/genetesting/Slide9>)
- Altered DNA, Altered Protein (<http://www.cancer.gov/cancertopics/understandingcancer/genetesting/Slide11>)

The Centre for Genetics Education offers a fact sheet about genetic changes that lead to disorders (<http://www.genetics.com.au/factsheet/03.htm>).

The University of Utah Genetic Science Learning Center also offers a discussion titled How Do Mutations Cause Genetic Disorders? (<http://gslc.genetics.utah.edu/units/disorders/proteinrole/>)

Do all gene mutations affect health and development?

No; only a small percentage of mutations cause genetic disorders—most have no impact on health or development. For example, some mutations alter a gene's DNA base sequence but do not change the function of the protein made by the gene.

Often, gene mutations that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed (makes a protein). Each cell has a number of pathways through which enzymes recognize and repair mistakes in DNA. Because DNA can be damaged or mutated in many ways, DNA repair is an important process by which the body protects itself from disease.

A very small percentage of all mutations actually have a positive effect. These mutations lead to new versions of proteins that help an organism and its future generations better adapt to changes in their environment. For example, a beneficial mutation could result in a protein that protects the organism from a new strain of bacteria.

For more information about DNA repair and the health effects of gene mutations:

The University of Utah Genetic Science Learning Center provides information about genetic disorders (<http://gslc.genetics.utah.edu/units/disorders/whataregd/>) that explains why some mutations cause disorders but others do not. (Refer to the questions in the far right column.)

Additional information about DNA repair is available from the NCBI Science Primer. In the chapter called What Is A Cell? (http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html), scroll down to the heading "DNA Repair Mechanisms."

What kinds of gene mutations are possible?

The DNA sequence of a gene can be altered in a number of ways. Gene mutations have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. The types of mutations include:

Missense mutation (illustration on page 8)

This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.

Nonsense mutation (illustration on page 9)

A nonsense mutation is also a change in one DNA base pair. Instead of substituting one amino acid for another, however, the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.

Insertion (illustration on page 9)

An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.

Deletion (illustration on page 10)

A deletion changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the resulting protein(s).

Duplication (illustration on page 10)

A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.

Frameshift mutation (illustration on page 11)

This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.

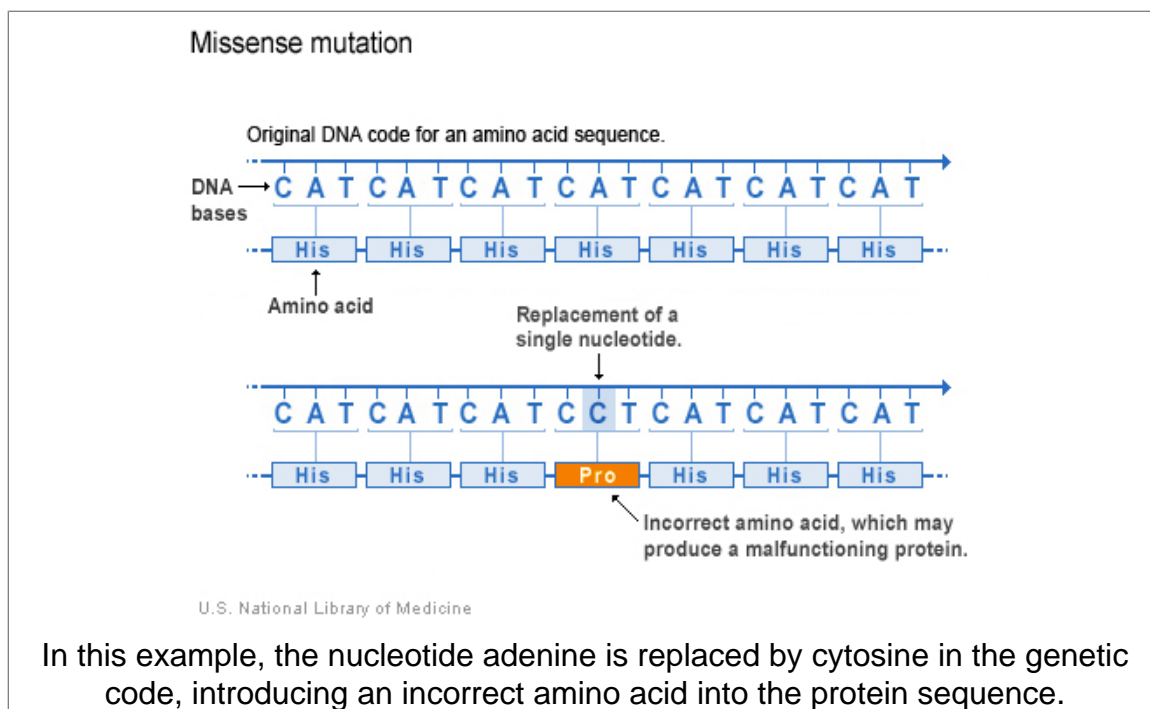
Repeat expansion (illustration on page 11)

Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function improperly.

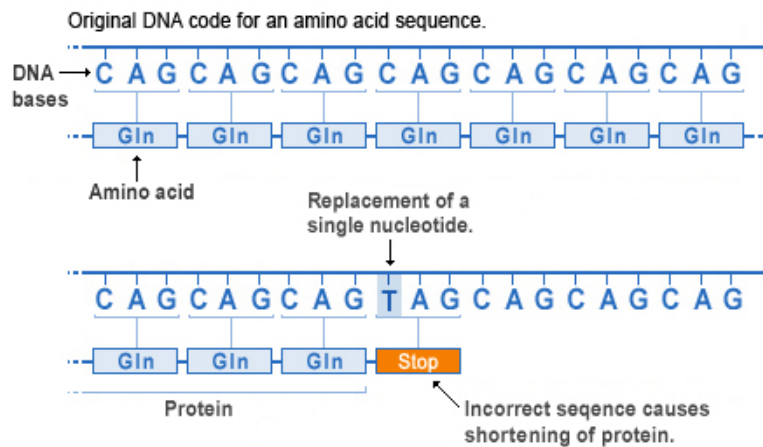
For more information about the types of gene mutations:

The National Human Genome Research Institute offers a Talking Glossary of Genetic Terms (<http://www.genome.gov/10002096>). This resource includes definitions, diagrams, and detailed audio descriptions of several of the gene mutations listed above.

Illustrations



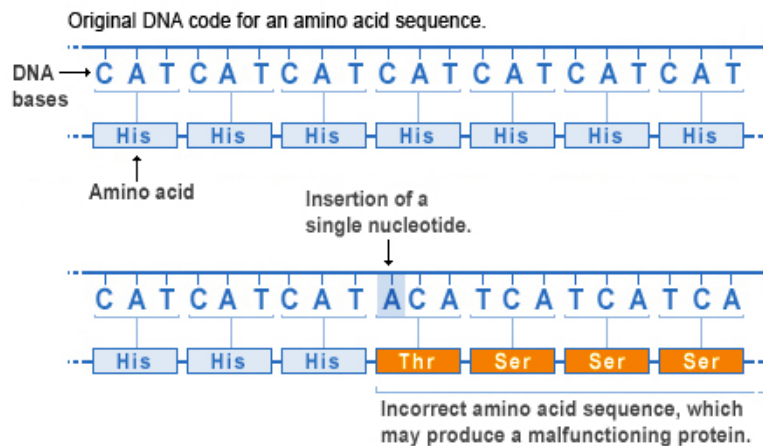
Nonsense mutation



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In this example, the nucleotide cytosine is replaced by thymine in the DNA code, signaling the cell to shorten the protein.

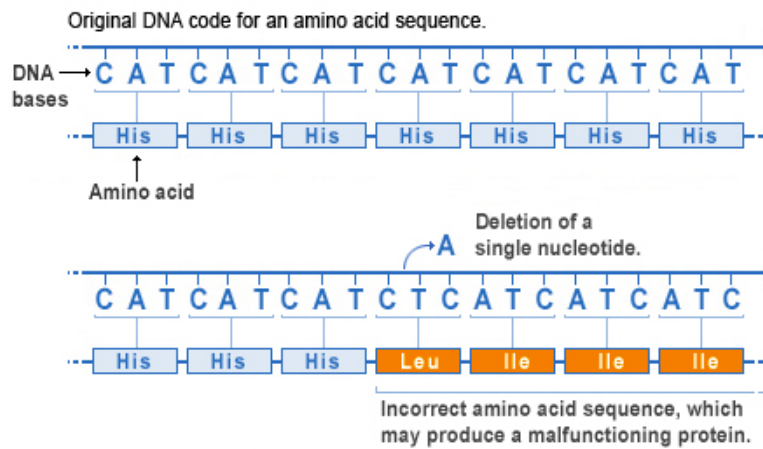
Insertion mutation



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In this example, one nucleotide (adenine) is added in the DNA code, changing the amino acid sequence that follows.

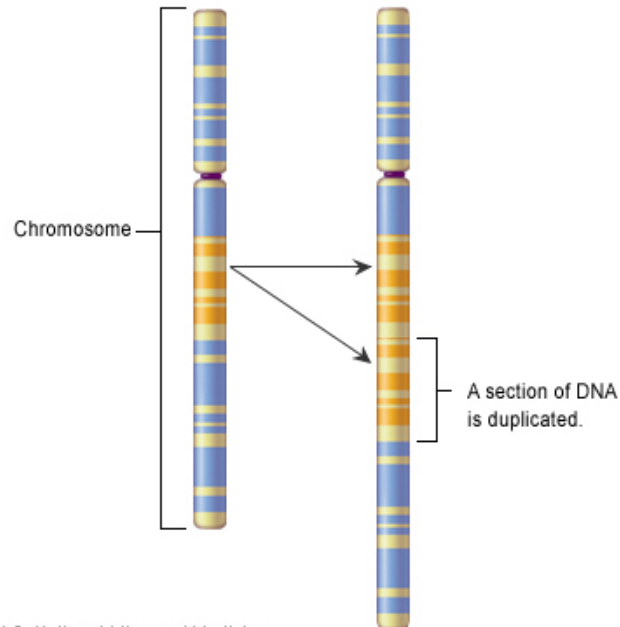
Deletion mutation



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In this example, one nucleotide (adenine) is deleted from the DNA code, changing the amino acid sequence that follows.

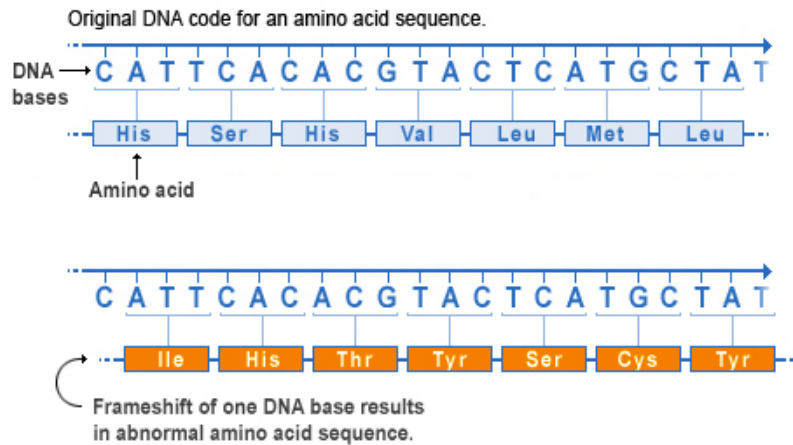
Duplication mutation



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A section of DNA is accidentally duplicated when a chromosome is copied.

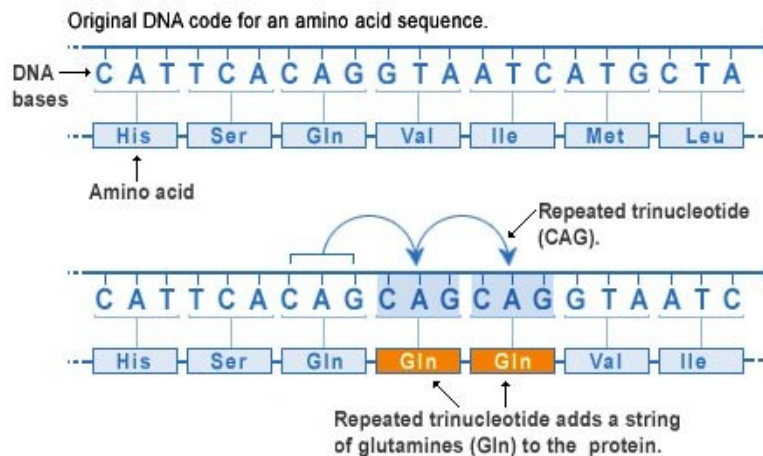
Frameshift mutation



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A frameshift mutation changes the amino acid sequence from the site of the mutation.

Repeat expansion mutation



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In this example, a repeated trinucleotide sequence (CAG) adds a series of the amino acid glutamine to the resulting protein.

Can changes in chromosomes affect health and development?

Changes that affect entire chromosomes or segments of chromosomes can cause problems with growth, development, and function of the body's systems. These changes can affect many genes along the chromosome and alter the proteins made by those genes. Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders.

Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes in each cell. A change in the number of chromosomes leads to a chromosomal disorder. These changes can occur during the formation of reproductive cells (eggs and sperm) or in early fetal development. A gain or loss of chromosomes from the normal 46 is called aneuploidy.

The most common form of aneuploidy is trisomy, or the presence of an extra chromosome in each cell. "Tri-" is Greek for "three"; people with trisomy have three copies of a particular chromosome in each cell instead of the normal two copies. Down syndrome is an example of a condition caused by trisomy—people with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

Monosomy, or the loss of one chromosome from each cell, is another kind of aneuploidy. "Mono-" is Greek for "one"; people with monosomy have one copy of a particular chromosome in each cell instead of the normal two copies. Turner syndrome is a condition caused by monosomy. Women with Turner syndrome are often missing one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

Chromosomal disorders can also be caused by changes in chromosome structure. These changes are caused by the breakage and reunion of chromosome segments when an egg or sperm cell is formed or in early fetal development. Pieces of DNA can be rearranged within one chromosome, or transferred between two or more chromosomes. The effects of structural changes depend on their size and location. Many different structural changes are possible; some cause medical problems, while others may have no effect on a person's health.

Many cancer cells also have changes in their chromosome number or structure. These changes most often occur in somatic cells (cells other than eggs and sperm) during a person's lifetime.

For more information about chromosomal disorders:

The National Human Genome Research Institute provides a list of questions and answers about chromosome abnormalities (<http://www.genome.gov/11508982>), including a glossary of related terms.

Chromosome Deletion Outreach offers a fact sheet on this topic titled Introduction to Chromosomes (<http://www.chromodisorder.org/intro.htm>).

The Genetics and Public Policy center also offers an overview of chromosomal mutations (<http://www.dnapolicy.org/genetics/geneticsAndDisease.jhtml.html#chromo>).

The Centre for Genetics Education provides fact sheets about changes in chromosome number or size (<http://www.genetics.com.au/factsheet/12.htm>) and chromosomal rearrangements (translocations) (<http://www.genetics.com.au/factsheet/13.htm>).

Additional information about chromosome abnormalities (http://genome.wellcome.ac.uk/doc_WTD020854.html) is available from the Wellcome Trust.

Can changes in mitochondrial DNA affect health and development?

Mitochondria (illustration on page 15) are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA (known as mitochondrial DNA or mtDNA). In some cases, inherited changes in mitochondrial DNA can cause problems with growth, development, and function of the body's systems. These mutations disrupt the mitochondria's ability to generate energy efficiently for the cell.

Conditions caused by mutations in mitochondrial DNA often involve multiple organ systems. The effects of these conditions are most pronounced in organs and tissues that require a lot of energy (such as the heart, brain, and muscles). Although the health consequences of inherited mitochondrial DNA mutations vary widely, frequently observed features include muscle weakness and wasting, problems with movement, diabetes, kidney failure, heart disease, loss of intellectual functions (dementia), hearing loss, and abnormalities involving the eyes and vision.

Mitochondrial DNA is also prone to noninherited (somatic) mutations. Somatic mutations occur in the DNA of certain cells during a person's lifetime, and typically are not passed to future generations. Because mitochondrial DNA has a limited ability to repair itself when it is damaged, these mutations tend to build up over time. A buildup of somatic mutations in mitochondrial DNA has been associated with some forms of cancer and an increased risk of certain age-related disorders such as heart disease, Alzheimer disease, and Parkinson disease. Additionally, research suggests that the progressive accumulation of these mutations over a person's lifetime may play a role in the normal process of aging.

For more information about conditions caused by mitochondrial DNA mutations:

Genetics Home Reference provides background information about mitochondria and mitochondrial DNA (<http://ghr.nlm.nih.gov/handbook/basics/mtdna>) written in consumer-friendly language.

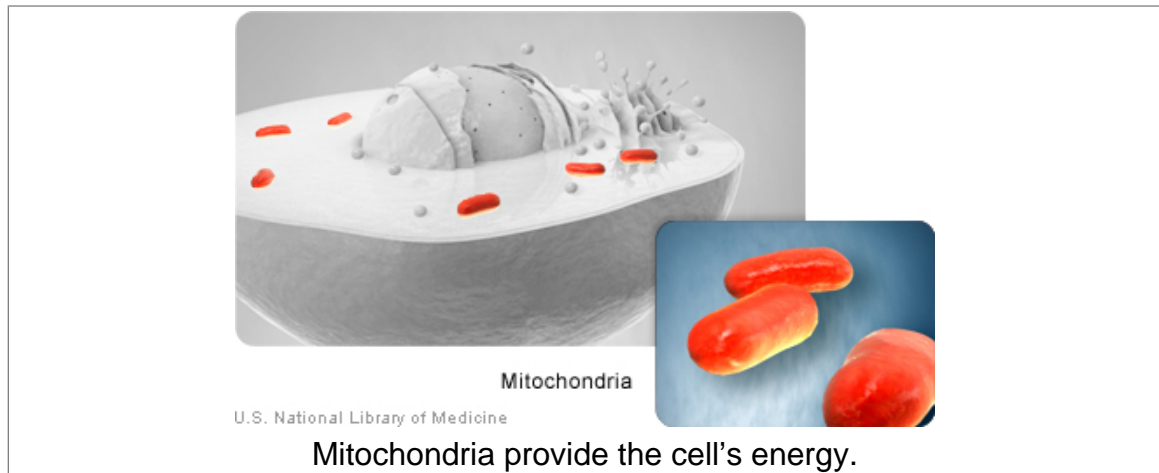
The Cleveland Clinic offers a basic introduction to mitochondrial disease (<http://www.clevelandclinic.org/health/health-info/docs/1600/1678.asp?index=6957>).

An overview of mitochondrial disorders (<http://www.genetests.org/query?dz=mt-overview>) is available from GeneReviews.

The Muscular Dystrophy Association offers an introduction to mitochondrial disorders as part of their fact sheet called Facts About Mitochondrial Myopathies (http://www.mdausa.org/publications/mitochondrial_myopathies.html#whatare).

The Neuromuscular Disease Center at Washington University provides an in-depth description of many mitochondrial conditions (<http://www.neuro.wustl.edu/neuromuscular/mitosyn.html#clinicalsyndromes>).

Illustrations



What are complex or multifactorial disorders?

Researchers are learning that nearly all conditions and diseases have a genetic component. Some disorders, such as sickle cell anemia and cystic fibrosis, are caused by mutations in a single gene. The causes of many other disorders, however, are much more complex. Common medical problems such as heart disease, diabetes, and obesity do not have a single genetic cause—they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Conditions caused by many contributing factors are called complex or multifactorial disorders.

Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. By 2010, however, researchers predict they will have found the major contributing genes for many common complex disorders.

For more information about complex disorders:

The University of Utah Genetic Science Learning Center provides information about multifactorial disorders (<http://gslc.genetics.utah.edu/units/disorders/whataregd/multi.cfm>) and a brief discussion of the complex basis of cancer.

The Wellcome Trust offers a fact sheet about polygenic and multifactorial disorders (http://genome.wellcome.ac.uk/doc_WTD020852.html). (Polygenic disorders are those related to the effects of more than one gene.)

A fact sheet about the inheritance of multifactorial disorders (<http://www.genetics.com.au/factsheet/10.htm>) is available from the Centre for Genetics Education.

If you would like information about a specific complex disorder such as diabetes or obesity, the National Institutes of Health offers a searchable list of health topics (<http://health.nih.gov/>) that will lead you to fact sheets and other reliable medical information. In addition, the Centers for Disease Control and Prevention provides a detailed list of diseases and conditions (<http://www.cdc.gov/node.do/id/0900f3ec8000e035>) that links to additional information.

What information about a genetic condition can statistics provide?

Statistical data can provide general information about how common a condition is, how many people have the condition, or how likely it is that a person will develop the condition. Statistics are not personalized, however—they offer estimates based on groups of people. By taking into account a person's family history, medical history, and other factors, a genetics professional can help interpret what statistics mean for a particular patient.

Some statistical terms are commonly used when describing genetic conditions and other disorders. These terms include:

Common statistical terms

| Statistical term | Description | Examples |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Incidence | The incidence of a gene mutation or a genetic disorder is the number of people who are born with the mutation or disorder in a specified group per year. Incidence is often written in the form “1 in [a number]” or as a total number of live births. | About 1 in 200,000 people in the United States are born with syndrome A each year. An estimated 15,000 infants with syndrome B were born last year worldwide. |
| Prevalence | The prevalence of a gene mutation or a genetic disorder is the total number of people in a specified group at a given time who have the mutation or disorder. This term includes both newly diagnosed and pre-existing cases in people of any age. Prevalence is often written in the form “1 in [a number]” or as a total number of people who have a condition. | Approximately 1 in 100,000 people in the United States have syndrome A at the present time. About 100,000 children worldwide currently have syndrome B. |
| Mortality | Mortality is the number of deaths from a particular disorder occurring in a specified group per year. Mortality is usually expressed as a total number of deaths. | An estimated 12,000 people worldwide died from syndrome C in 2002. |
| Lifetime risk | Lifetime risk is the average risk of developing a particular disorder at some point during a lifetime. Lifetime risk is often written as a percentage or as “1 in [a number].” It is important to remember that the risk per year or per decade is much lower than the lifetime risk. In addition, other factors may increase or decrease a person’s risk as compared with the average. | Approximately 1 percent of people in the United States develop disorder D during their lifetimes. The lifetime risk of developing disorder D is 1 in 100. |

For more information about understanding and interpreting statistics:

The New York Department of Health provides a basic explanation of statistical terms (<http://www.health.state.ny.us/diseases/chronic/basicstat.htm>), including incidence, prevalence, morbidity, and mortality.

Information about interpreting cancer statistics (<http://www.cdc.gov/excite/skincancer/mod04.htm>) is available from the Centers for Disease Control and Prevention (CDC) as part of an educational module for students. Although this information focuses on cancer, information about health statistics can also apply to other disorders. The National Cancer Institute offers additional tools for understanding cancer statistics (<http://www.nci.nih.gov/statistics/understanding>).

How are genetic conditions and genes named?

Naming genetic conditions

Genetic conditions are not named in one standard way (unlike genes, which are given an official name and symbol by a formal committee). Doctors who treat families with a particular disorder are often the first to propose a name for the condition. Expert working groups may later revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately help researchers find new approaches to treatment.

Disorder names are often derived from one or a combination of sources:

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency);
- One or more major signs or symptoms of the disorder (for example, sickle cell anemia);
- The parts of the body affected by the condition (for example, retinoblastoma);
- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome, which was named after Dr. Antoine Bernard-Jean Marfan);
- A geographic area (for example, familial Mediterranean fever, which occurs mainly in populations bordering the Mediterranean Sea); or
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis, which is also called Lou Gehrig disease after a famous baseball player who had the condition).

Disorders named after a specific person or place are called eponyms. There is debate as to whether the possessive form (e.g., Alzheimer's disease) or the nonpossessive form (Alzheimer disease) of eponyms is preferred. As a rule, medical geneticists use the nonpossessive form, and this form may become the standard for doctors in all fields of medicine. Genetics Home Reference uses the nonpossessive form of eponyms.

Genetics Home Reference consults with experts in the field of medical genetics to provide the current, most accurate name for each disorder. Alternate names are included as synonyms.

Naming genes

The HUGO Gene Nomenclature Committee (<http://www.gene.ucl.ac.uk/nomenclature/>) (HGNC) designates an official name and symbol (an abbreviation

of the name) for each known human gene. Some official gene names include additional information in parentheses, such as related genetic conditions, subtypes of a condition, or inheritance pattern. The HGNC is a non-profit organization funded by the U.K. Medical Research Council and the U.S. National Institutes of Health. The Committee has named more than 13,000 of the estimated 20,000 to 25,000 genes in the human genome.

During the research process, genes often acquire several alternate names and symbols. Different researchers investigating the same gene may each give the gene a different name, which can cause confusion. The HGNC assigns a unique name and symbol to each human gene, which allows effective organization of genes in large databanks, aiding the advancement of research. For specific information about how genes are named, refer to the HGNC's Guidelines for Human Gene Nomenclature (<http://www.gene.ucl.ac.uk/nomenclature/guidelines.html>).

Genetics Home Reference describes genes using the HGNC's official gene names and gene symbols. Genetics Home Reference frequently presents the symbol and name separated with a colon (for example, FGFR4: fibroblast growth factor receptor 4).



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Handbook
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| Chapter | Last Comprehensive Review |
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